Occupational Asthma: A Review

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Occupational asthma is the most common form of occupational lung disease in the developed world at the present time. In this review, the epidemiology, pathogenesis/mechanisms, clinical presentations, management, and prevention of occupational asthma are discussed. The population attributable risk of asthma due to occupational exposures is considerable. Current understanding of the mechanisms by which many agents cause occupational asthma is limited, especially for low-molecular-weight sensitizers and irritants. The diagnosis of occupational asthma is generally established on the basis of a suggestive history of a temporal association between exposure and the onset of symptoms and objective evidence that these symptoms are related to airflow limitation. Early diagnosis, elimination of exposure to the responsible agent, and early use of inhaled steroids may play important roles in the prevention of long-term persistence of asthma. Persistent occupational asthma is often associated with substantial disability and consequent impacts on income and quality of life. Prevention of new cases is the best approach to reducing the burden of asthma attributable to occupational exposures. Future research needs are identified. *Key words*: asthma, immunologic, irritant-induced, nonimmunologic, occupational, prevention, reactive airways dysfunction syndrome, sensitizer-induced, work-related. — *Environ Health Perspect* 108(suppl 4):697–704 (2000).
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Work-related asthma is the most common form of occupational lung disease, causing significant morbidity and disability. Work-related asthma may be categorized into occupational asthma, which refers to new-onset asthma caused by exposure at the workplace, and work-aggravated asthma, in which preexisting asthma is exacerbated.

In this review, the epidemiology, pathogenesis/mechanisms, and clinical presentations of occupational asthma (both sensitizer- and irritant-induced) are discussed. A diagnostic approach is presented, including history and exposure assessment, physical examination, and objective tests used to confirm both the diagnosis and work-relatedness of asthma. Management of the worker with occupational asthma is also addressed, including work modifications, prognosis, and impairment/disability assessment. Finally, the prevention of occupational asthma and future research needs are highlighted.

Definition/Classification of Occupational Asthma

Workplace exposure is an important cause of both new-onset asthma and exacerbations of preexisting disease. Although the term occupational asthma usually refers to new-onset asthma caused by exposure at the workplace, exacerbations of preexisting asthma are a potentially more important cause of morbidity because there are more workers with work-aggravated asthma than work-caused asthma.

How the various types of work-related asthma are defined often depends on the setting (e.g., epidemiologic research, disease surveillance, or workers' compensation). An accepted operational definition of occupational asthma for clinical purposes is variable airflow limitation and/or airway hyperresponsiveness due to exposure to a specific agent or conditions in a particular work environment and not to stimuli encountered outside the workplace (*1*). This definition includes no reference to the mechanism of asthma induction, and therefore work-related variable airway obstruction caused by antigen-induced hypersensitivity reactions, pharmacologic effects, nonspecific inflammatory processes, and direct airway irritation can qualify as occupational asthma. In the past, the term occupational asthma often was used to refer only to patients with reversible airflow limitation due to sensitization to a substance encountered at work (i.e., immunologic or sensitizer-induced asthma) that involves a latent period. With such an approach, workers who develop persistent symptoms of asthma and nonspecific airway hyperresponsiveness promptly after short-term, high-intensity inhalational exposure to irritant materials would not be considered to have occupational asthma. The term reactive airways dysfunction syndrome (RADS) has been coined to refer to this condition (*2*).

Recently, a consensus appears to be developing around the concept that there is a nonimmunologic type of occupational asthma (without latency) that may occur after single or multiple exposures to nonspecific irritant chemicals at concentrations high enough to induce airway injury and inflammation (*1,3*). Because RADS refers only to asthma occurring after a single high-intensity exposure, the term irritant-induced asthma is used in this paper. Recurrent exposure to an irritant before the onset of asthmatic symptoms may lead to blurring of the distinction based on latency.

Another type of disorder characterized by work-related variable airways limitation is associated with occupational exposure to organic dusts such as cotton, flax, hemp, jute, sisal, and various grains. Many but not all occupational lung disease experts consider organic dust-induced airways disease to be an asthmalike disorder rather than true asthma (*1*). Reasons for this distinction include lack of airway eosinophilia, less frequent airway hyperresponsiveness, and a tendency to develop chronic bronchitis (by clinical definition) and chronic airflow limitation with chronic exposure.

Occupational asthma may need to be approached differently for epidemiologic and disease surveillance purposes than for medical–legal purposes. An inclusive approach is appropriate for use in a surveillance system in which identification triggers an investigation or intervention. If prevention of work-related asthma disability and loss of productivity is the goal, then variable airflow limitation and/or airway hyperresponsiveness caused or aggravated by exposures at the workplace must be considered.

Epidemiology

Reports from several surveillance programs have suggested that occupational asthma is probably the most common type of occupational lung disease in industrialized countries. Occupational asthma accounted for 26% of all work-related respiratory disease reported to the Surveillance of Work and Occupational Respiratory Disease (SWORD) program in the United Kingdom (*4*) and 52% of such cases in British Columbia, where there is a particularly high prevalence due to the use of western red cedar (*5*). The overall prevalence of occupational asthma in the general population, however, is not clearly known. In the United States, analysis of 1978 Social Security disability data indicated that approximately

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15% of individuals disabled from asthma attributed it to workplace exposures (*6*).

A number of studies have attempted to address the issue of attributable risk of asthma or wheezing in the general population due to occupation (i.e., what fraction of all asthma is due to occupational exposures?). This issue is complicated by the acknowledged lack of a standardized definition of asthma. A recent review of the existing literature on the population attributable risk of asthma due to occupational exposures provided a range from 8 to 21% depending on the definition of exposure (*7*).

The prevalence of occupational asthma in various occupational cohort studies depends on the agent(s) to which the workers are exposed, levels of exposure, and host suseptibility factors such as atopy and cigarette smoking. The highest prevalences of occupational asthma have been reported with exposures to platinum salts and proteolytic enzymes used in the detergent industry (up to 50%) (*8,9*). In general, however, the prevalence of occupational asthma in most cohorts of workers exposed to a known sensitizing agent is less than 10% (*10*). There are convincing data to indicate that the level of exposure is an important risk factor for sensitizer-induced occupational asthma (*10*).

Atopy appears to be an important risk factor for occupational asthma due to IgE-dependent mechanisms. Psyllium workers (*11*), bakers (*12*), and laboratory animal handlers (*13*) who are atopic have been shown to be at increased risk of developing occupational asthma compared to their non-atopic co-workers. Cigarette smoking also appears to increase risk of IgE-mediated occupational asthma. Workers who smoke and have been exposed to platinum salts, acid anhydrides, snow crab, green coffee beans, and ispaghula have been shown to have greater risk of developing occupational asthma than their nonsmoking coworkers (*14*). In contrast, for most sensitizing agents that cause asthma through mechanisms not involving specific IgE antibodies, such as diisocyanates and western red cedar, atopy and smoking do not appear to be risk factors (*15,16*).

Little is known about the epidemiology of irritant-induced asthma, but it is likely a relatively rare outcome of irritant exposure. SWORD data suggest that < 10% of reported inhalational injuries are followed by persistent asthma (*17*). Irritant exposures may deserve greater attention as important preventable causes of occupational asthma. Recent data from the Sentinel Health Notification System for Occupational Risk (SENSOR) program in the United States indicate that exposures to irritants are reported as frequently as exposures to sensitizers as causes of new-onset asthma (*18*). Level of exposure is likely to be a risk factor for irritant-induced asthma. In a study of hospital laboratory workers exposed to a spill of glacial acetic acid, the risk of irritant-induced asthma increased with level of exposure as assessed by distance from the spill (*19*). Several studies have also suggested that atopy and smoking are risk factors for irritant-induced asthma (*20,21*).

Pathogenesis/Mechanisms

Immunologic or Sensitizer-Induced Occupational Asthma

More than 250 agents have been adequately documented as causing immunologic occupational asthma (*22*). Table 1 lists some of the more common agents and workers at risk. The mechanisms of sensitization by which these agents induce asthma can be somewhat arbitrarily divided based on molecular weight of the agents. High-molecular-weight (HMW) compounds (≥ 5,000 Da) and some low-molecular-weight (LMW) compounds (< 5,000 Da), such as platinum salts and acid anhydrides induce asthma by specific IgE antibody-dependent reactions. However, use of the term immunologic does not necessarily imply an IgE-mediated response and cell-mediated responses may be involved. IgE antibodies specific for the sensitizing agent in the workplace frequently cannot be demonstrated in cases of occupational asthma caused by LMW compounds such as diisocyanates and plicatic acid (the agent responsible for causing asthma in workers exposed to western red cedar).

Whereas HMW compounds act as complete antigens, LMW compounds must react with proteins (autologous or heterologous) to produce a complete antigen. In IgE-mediated occupational asthma, inhaled sensitizers bind to specific IgE on the surface of mast cells, basophils, and probably macrophages, eosinophils, and platelets. The specific reaction between allergen and IgE causes a cascade of events that produces the activation of inflammatory cells. Mast-cell activation leads to early bronchoconstriction as a result of preformed mediator release (e.g., histamine; leukotrienes C_4, D_4, and E_4; and prostaglandin D_2). IgE-dependent activation of mast cells also leads to release of multiple cytokines/chemokines and increased expression of various adhesion molecules that are involved in modulating the late inflammatory reaction after allergen exposure.

As noted previously, for a number of LMW compounds, specific IgE compounds either have not been found or have been found only in a subset of affected workers. A recent study using basophils from patients with western red cedar showed that plicatic acid did not induce histamine release from basophils by a tyrosine kinase-mediated mechanism as would be expected in an IgE-dependent response (*23*). However, in a companion study, it was shown that T lymphocytes from such patients specifically responded to a conjugate of plicatic acid and human serum albumin, suggesting an underlying immunologic mechanism (*24*).

Whether immunologic occupational asthma is induced by HMW or LMW sensitizers, T cells appear to play an important role in the orchestration of the inflammatory process, and eosinophils, mast cells, epithelial cells, and neutrophils are the main effector cells that produce the characteristic features of asthma (i.e., smooth muscle contraction, mucus hypersecretion, airway inflammation, and epithelial injury). It has been hypothesized that allergic asthma is driven and maintained by the persistence of a specialized subset of chronically activated

Table 1. Selected major causes of occupational asthma and workers at risk.

Agents	Workers at risk
Animals	
Animal proteins	Animal handlers, laboratory research workers
Prawns, crabs	Processors of these foods
Egg protein	Egg producers
Plants	
Grain dust	Grain storage workers
Wheat, rye, soy flours	Bakers, millers
Latex	Health-care workers
Green coffee bean	Coffee roasters
Enzymes	
Proteases from *Bacillus subtilis*	Detergent industry workers
Pancreatin, papain, pepsin	Pharmaceutical industry workers
Fungal amylase	Bakers
Wood dusts	
Western red cedar, redwood	Sawmill workers, joiners, carpenters
Chemicals	
Diisocyanates	Polyurethane, plastics, varnish workers
Acid anhydrides	Epoxy resins, alkyd resins, plastics workers
Complex amines	Photographers, shellac workers, painters
Azodicarbonamide	Plastics, rubber workers
Reactive dyes	Textile workers
Methyl methacrylate	Health-care workers
Drugs	
Penicillins, psyllium, cimetidine	Pharmaceutical industry, health-care workers
Metals	
Platinum salts	Platinum-refining workers
Cobalt	Hard-metal grinders
Chromium, nickel	Metal-plating workers
Other	
Metal-working fluids	Machinists
Aluminum potroom emissions	Aluminum-refining workers
Colophony in solder flux	Electronics workers

T memory cells sensitized against aeroallergenic, occupational, or viral antigens. Studies showing proliferation of peripheral-blood lymphocytes after stimulation with cobalt and nickel (*25*) or diisocyanates (*26*) in sensitized subjects support this hypothesis. In nonoccupational allergic asthma, the majority of T-cell clones derived from the bronchial mucosa are $CD4^+$, whereas in diisocyanate-induced asthma, the majority are $CD8^+$ (*27*). Interestingly, an increased percentage of $CD8^+$ T cells and increased production of interleukin (IL)-5 have been found in bronchoalveolar lavage fluid from nonatopic asthmatics (*28*).

Recent investigations into the genetic determinants of risk for sensitizer-induced occupational asthma suggest that polymorphisms in genes encoding major histocompatibility complex (MHC) class II proteins may be important determinants of the specificity of response to sensitizing agents. In workers with exposure to diisocyanates, HLA-DQB1*0503 and DQB1*0201/0301 alleles are associated with asthma, whereas HLA-DQB1*0501 and DQA1*0101-DQB1*0501-DR1 appear to be protective (*29*). The alleles, HLA-DQB1*0503 and HLA-DQB1*0501, differ at residue 57 for a single amino acid, aspartic acid in DQB1*0503 and valine in DQB1*0501, suggesting that residue 57 may be a potentially critical location in the development of asthma (*30*). Associations with MHC proteins have also been described in acid anhydride-induced asthma (*31*), in platinum salts-induced asthma, and in red cedar-induced asthma (*32*). The DRB1*13 marker was associated with the risk of soybean epidemic asthma in Barcelona, Spain (*33*), and the phenotype frequencies of DR1 and DR4 are slightly increased in subjects sensitized to latex (*34*).

Nonimmunologic or Irritant-Induced Occupational Asthma

The mechanisms of irritant-induced asthma are largely unknown, but a localized airway inflammatory response is likely involved. It is important to note that most patients who have sustained a toxic inhalational injury to their airways (chemical bronchitis) will recover without developing asthma. There are bronchial biospy data from patients who developed clinically evident asthma after exposure to high concentrations of irritants (e.g., RADS) that suggest that the histopathologic changes are similar to those of typical asthma, i.e., subepithelial fibrosis and infiltration of the mucosa/submucosa by eosinophils and T cells. However, the fibrosis tends to be greater and the T-cell infiltration/activation tends to be less (*2,35,36*).

It has been hypothesized that irritant-induced epithelial damage is followed by direct activation of nonadrenergic, noncholinergic pathways via axon reflexes and onset of neurogenic inflammation (*37*). Nonspecific macrophage activation and mast cell degranulation may also occur. Recruitment of other inflammatory cells likely enhances the inflammatory response. The damaged bronchial epithelium may contribute to the persistence of the inflammatory response by release of proinflammatory mediators but also may exhibit impaired function (e.g., reduced neutral endopeptidase activity, decreased generation of epithelial-derived relaxing factor). Irritant-induced airway inflammation may alter epithelial permeability such that subepithelial irritant receptors are more likely to be exposed to nonspecific stimuli such as cold air, exercise, cigarette smoke, and other inhaled irritants. Stimulation of these receptors may further increase the likelihood of persistence of airway inflammation and nonspecific airway hyperresponsiveness. Recovery from irritant-induced asthma appears to occur over time in many cases. However, the greater the initial injury, the more unlikely that complete recovery will occur. With severe injury, whether after a single high-concentration inhalation or multiple low-concentration exposures, there may be sufficient airway remodeling (i.e., deposition of type III collagen under the basement membrane) that complete recovery cannot occur.

Although much has been learned about the pathogenetic mechanisms underlying the various types of occupational asthma, little of this information has clinical applicability at this point because of important data gaps. This caveat is especially relevant to the issue of testing of workers for genetic susceptibility. Such testing cannot be recommended because there is not sufficient understanding of the interactions among genetic and environmental determinants of risk of occupational asthma.

Diagnosis

The diagnosis of occupational asthma is made by confirming the diagnosis of asthma and by establishing a relationship between asthma and work (*38–41*). Occupational asthma should be considered in every case of adult-onset asthma or asthma that worsens in adult life (*15,40*).

Making a diagnosis of asthma requires the presence of both intermittent respiratory symptoms (e.g., cough, wheezing, chest tightness, and/or dyspnea) and physiologic evidence of reversible/variable airways obstruction or hyperresponsiveness. After the diagnosis of asthma is confirmed, the next step is to assess the patient's relationship with work, preferably by means of objective tests. In general, the patient's history alone is not sufficient for the diagnosis of occupational asthma and is more likely to exclude than to confirm the diagnosis of occupational asthma (*38,42*). Objective confirmation of the diagnosis is necessary for both appropriate medical care and compensation purposes. It is important to recognize that no single test can be used to confirm the diagnosis in all cases.

Clinical Picture

Patients with occupational asthma may present with varying degrees of respiratory compromise, from mild symptoms to moderate or severe bronchospasm. In general, occupational asthma presents clinically in the same way as asthma of non-occupational origin. Mild cases of asthma may present with only episodic dry cough, chest tightness, and increased breathing effort. Signs and symptoms in more severely affected patients include wheezing, cough, chest tightness, shortness of breath, and dyspnea on exertion. Some patients with occupational asthma develop work-related bronchitis, characterized by recurrent episodes of cough and sputum production. Others may experience nocturnal awakening as an early manifestation of occupational asthma.

Rhinoconjunctivitis, which is manifested by ocular and nasal discharge and pruritus, and sneezing, may accompany respiratory symptoms. In a study comparing the occurrence of rhinoconjunctivis symptoms in workers exposed to HMW versus LMW substances, it was found that rhinoconjunctivitis occurred prior to the onset of occupational asthma in workers exposed to HMW substances; those exposed to LMW substances developed symptoms concurrently with their respiratory symptoms. It was postulated that HMW substances are more likely to invoke IgE-mediated immune responses that result in this temporal symptom pattern (*43*).

In immunologic or sensitizer-induced occupational asthma, symptoms typically develop months or years after the onset of exposure. Substances that cause sensitizer-induced asthma may induce early, late, or dual airway responses (Figure 1). An early asthmatic reaction begins within a few minutes of inhalation, with maximal bronchoconstriction occurring within 30 min. Late asthmatic reactions occur within 4–8 hr of inhalation. Dual, or biphasic, asthmatic reactions are characterized by both early and late bronchoconstriction. IgE-dependent agents such as HMW substances, may induce both early and biphasic reactions (*15,44*). IgE-independent agents are more likely to induce late or biphasic reactions (*15,44*). These patterns of airway responses are most clearly demonstrated in controlled exposure settings rather than in typical workplace settings, which are more likely to

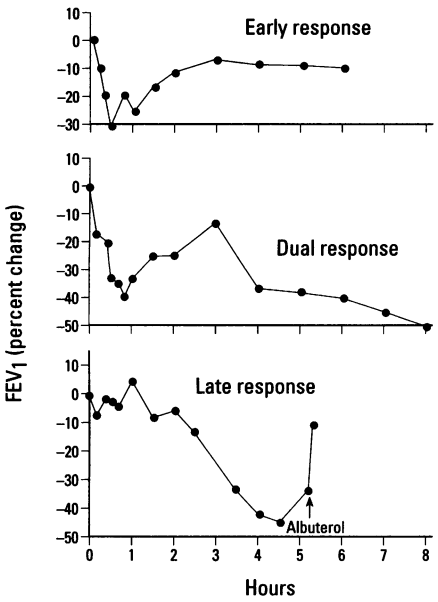

Figure 1. Potential responses to inhaltion of sensitizing agent in patients with immunologic occupational asthma.

involve exposures that vary over the course of the day and work week.

Nonimmunologic or irritant-induced asthma is caused by exposure to gases, fumes, mists, smoke, or dusts that are directly irritating to the airways. Chemical bronchitis often precedes the development of irritant-induced asthma. In RADS, asthmatic symptoms occur relatively promptly and persistently after a single, high-concentration inhalational exposure. In irritant-induced asthma involving multiple lower-concentration exposures, while recurrent symptoms of mucosal irritation are often experienced earlier, symptoms of asthma may be more gradual in onset.

History and Exposure Assessment

As in the evaluation of any patient with a possible work-related injury or illness, the evaluation of occupational asthma includes a detailed medical and occupational history. In the history of the present illness, the temporal relationship between recent exposures and respiratory symptoms must be investigated. A relationship between asthmatic symptoms and workplace exposures is suggested if any of the following patterns are present: symptoms that occur only at work; symptoms that improve on weekends or vacations; symptoms that occur regularly after the workshift; symptoms that progressively increase over the course of the work week; and symptoms that improve after a change in the work environment (*39*).

Potential exposures to all "asthmagens" in the workplace as well as the home environment should be assessed. Workers also must be queried regarding any jobs in addition to their full-time employment and/or hobbies that might expose them to other asthmagens. Specific occupational history questions include not only the job title of the worker but also specific job duties performed. In event of accidents or spills, information regarding the role the worker played, proximity to the point source, size of the room, ventilation, duration of exposure, and type and efficacy of respiratory protection, i.e., personal protective equipment, should be evaluated. Evaluation also should include assessing the intensity or magnitude of exposure including review of available industrial hygiene records, types of industrial processes used, such as those involving chemicals with high vapor pressure or heating; job characteristics such as spray painting, and geographic and climactic factors. In addition, other workers who have developed episodic respiratory symptoms must be identified, and their complete chronologic occupational histories obtained.

Past medical histories should focus on any history of asthma, including current and past medications, (e.g., frequency of use, patterns of use in relation to work), a history of hospitalizations or emergency room evaluations, and intubations. Other pertinent history includes childhood asthma, allergic rhinitis, atopic dermatitis, and other respiratory conditions such as chronic obstructive pulmonary disease. Cardiac history, including angina, and gastrointestinal history, including gastroesophageal reflux, which may present with episodic dyspnea, must also be evaluated. A history of allergies, previous allergy testing, and cigarette smoking should be assessed, as should a history of airway hyperresponsiveness to nonallergenic stimuli such as exercise, cold air, or irritants.

Physical Examination

The physical examination of a patient with asthma is frequently completely normal. Physical examination should be focused on the upper and lower respiratory tract, including visualizing nasal and oropharyngeal mucous membranes, palpating the sinuses, and inspecting for nasal polyps. The chest should be auscultated during quiet breathing and forced exhalation, noting wheezes, rhonchi, or crackles. Cardiac examination should be performed to exclude a cardiac etiology for respiratory distress. The skin should be inspected for eczematous dermatitis and the extremities inspected for clubbing, cyanosis, and edema.

Objective Tests

Most asthmatic patients have normal chest radiographs because asthma involves the airways rather than the lung parenchyma. During exacerbations, hyperinflation and flattening of the diaphragms may be visualized because of air trapping. Bronchial wall thickening, reflecting chronic inflammation, and mucus plugging, manifested by fleeting infiltrates, may be observed.

As there are no physical examination findings specific for asthma and work-related wheezing is difficult to detect, repeated pulmonary function testing (both at and away from work) is usually required to make the diagnosis of occupational asthma. Spirometry, both pre- and post-bronchodilator, is the most reliable method of determining the presence of airflow limitation. It can be used to measure the response to a bronchodilator, which generally confirms the diagnosis of asthma. The American Thoracic Society defines a 12% improvement in the FEV_1 (forced expiratory volume in 1 sec) or an absolute value increase of at least 200 mL after bronchodilator administration as evidence of reversibility of airflow limitation (*45*). A decrease of 10% in the FEV_1 across a work shift is objective evidence for work-related bronchoconstriction (*46*).

Peak expiratory flow (PEF), which is measured in liters/minute via a hand-held peak flow meter, is a simple and inexpensive method to assess airflow limitation and can be performed by the patient outside medical or work settings. The patient is instructed to exhale as forcefully as possible into this device, preferably at least four times per day, prior to work, during various times in the work shift, after work, and prior to bedtime. In addition, the patient is asked to maintain a symptom diary, recording the time of day, the PEF reading, and any respiratory symptoms; these are evaluated by a physician on medical follow-up. At least 2 weeks of serial PEF recordings are needed to assess whether occupational asthma is likely. A 20% or greater diurnal variability in PEF has been used to diagnose workers with occupational asthma and a computerized system of analysis is under development, but at present, visual inspection of whether there is a work-related pattern of increased diurnal variability is probably the best approach to the analysis of serial peak flow recordings (*38,47*).

Currently there is debate about whether PEF readings are accurate, as they are dependent on patient effort and reliability. In a study of 17 subjects instructed in the use of a portable computerized peak flow meter who were unaware that their readings were being stored by the flow meter, it was found that only 55% of the records were completely accurate in terms of the recorded value and timing of the measurements (*48*). Worker training may improve the accuracy of measurements (*49*) and portable computerized peak flow meters are becoming increasingly affordable. Despite concerns about accuracy of patient-recorded PEF

data, some investigators have found such data to have reasonable sensitivity and specificity for the diagnosis of occupational asthma (*47,50*).

In a worker suspected of having occupational asthma but who has normal spirometry, inhalation challenge testing with methacholine or histamine can demonstrate the presence of nonspecific airway hyperresponsiveness. Progressive doses of histamine or methacholine are administered to the patient and serial FEV_1 measurements are obtained to generate a dose–response curve. The PC20 is the provocative concentration of histamine or methacholine that induces a 20% drop in FEV_1, after which the test is terminated. This test can be performed on an outpatient basis and several published protocols are available (*51*). On occasion, workers with occupational asthma do not show clear evidence of work-related lung function changes until after a prolonged period of removal from the causative exposure. In other words, it may take several weeks away from the usual workplace before noticeable improvement is noted in the patient's spirometry, PEF, and/or methacholine responsiveness.

Specific inhalation challenge tests, also called specific bronchial provocation studies, are rarely performed in the United States. When performed, the purpose of a specific challenge is often to determine the precise etiology in a complex exposure scenario or to investigate an unreported sensitizer. Historically, a specific inhalation challenge test has been considered a potentially dangerous procedure because the specific agent thought to induce occupational asthma is administered to the subject. These should be administered in a tightly controlled situation with careful monitoring in a hospital setting. However, recent studies in Quebec indicate that if stringent exposure and safety protocols are followed, specific inhalation challenge tests can be performed with minimal risk to the subjects (*52*).

Atopy, which is a risk factor for HMW sensitizer-induced asthma, can be established by administering skin prick tests with common aeroallergens. Extracts are available for confirming immediate hypersensitivity to some occupational sensitizers such as flour, animal proteins, and coffee. Patients can also be tested for the presence of specific IgE antibodies against HMW and some LMW sensitizers (diisocyanates, acid anhydrides).

Diagnostic Criteria

As noted previously, the diagnosis of occupational asthma involves confirming the diagnosis of asthma and suggested work-relatedness. The American College of Chest Physicians suggested the following criteria in 1995 for establishing a diagnosis of occupational asthma: a history compatible with occupational asthma; the presence of airflow limitation and its reversibility; in the absence of airflow limitation, the presence of nonspecific airway hyperresponsiveness; and the demonstration of work-relatedness of asthma by objective means (*38*). The Canadian Thoracic Society has suggested a similar approach in making the diagnosis of occupational asthma, by demonstrating the presence of asthma with pulmonary function tests and then assessing the relationship between asthma and work (*40*).

The National Institute for Occupational Safety and Health has recently updated its surveillance case definition and surveillance classification criteria for its state-based SENSOR programs for work-related asthma, which currently exist in California, Massachusetts, Michigan, and New Jersey (*17*). Sentinel health events, which include cases of work-related asthma, indicate the need for preventive measures. Surveillance of work-related asthma may be accomplished by requiring health care professionals to report all diagnosed or suspected cases to state health departments. In analysis of these cases, the relative frequencies of classes of work-related asthma can be determined, as can gender frequencies, specific asthma-inducing agents, whether previously known or newly discovered, and the most common industries in which workers develop work-related asthma.

The SENSOR surveillance case definition for state health departments for work-related asthma includes: *a*) a health care professional's diagnosis consistent with asthma, and *b*) an association between symptoms of asthma and work. The SENSOR programs classify work-related asthma into three broad categories by using surveillance case classification criteria. These classes include occupational asthma, or work-induced asthma which is new in onset; work-aggravated asthma, which occurs in workers with preexisting asthma that has been treated within the past two years; and RADS, or irritant-induced asthma. The SENSOR case classification criteria are as follows:

- Work-aggravated asthma is defined as preexisting asthma that was symptomatic and/or treated with asthma medication within the 2 years prior to entering the occupational setting associated with the patient's asthma symptoms.
- RADS is defined as new asthma symptoms that develop within 24 hr after a one-time high-level inhalation exposure (at work) to an irritant gas, fume, smoke, or vapor and that persist for at least 3 months.
- Occupational or work-induced asthma is defined as:
  a) workplace exposure to an agent previously associated with occupational asthma; or
  b) work-related changes in serially measured FEV_1 or PEF; or
  c) work-related changes in bronchial responsiveness as measured by serial nonspecific inhalation challenge testing; or
  d) positive response to specific inhalation challenge testing with an agent to which the patient has been exposed at work.

Although the SENSOR surveillance case definition and classification criteria were designed for specific epidemiologic purposes, they provide a reasonable approach for the clinical evaluation of patients.

Management

The mainstay of treatment for occupational asthma is prompt diagnosis and removal of the worker from further exposure to the inciting agent if substitution with a less hazardous substance is not possible (*15,38–40,44*). This is crucial in cases of sensitizer-induced occupational asthma, as very low exposures may trigger asthmatic reactions including status asthmaticus. Substances such as toluene diisocyanate have been reported to induce asthma in sensitized workers in the parts-per-billion range. Workers with irritant-induced or work-aggravated asthma may continue to work in their usual jobs if their exposure to the inciting agent is diminished through proper engineering controls or respiratory protective equipment if engineering controls are not feasible.

General Asthma Management

Patients diagnosed with occupational asthma should have medical management following published guidelines (*53*). Since asthma is characterized by airway inflammation, inhaled corticosteroids have become a mainstay of treatment. Malo and colleagues (*54*) demonstrated that inhaled corticosteroids induce a small but significant overall improvement after withdrawal from exposure of patients with sensitizer-induced occupational asthma due to both HMW and LMW agents. In their double-blind crossover study, it was found that inhaled steroids were more beneficial if administered earlier rather than later after the diagnosis of occupational asthma.

Work Implications and Prognosis

Occupational asthma can become a very disabling disease, resulting in long-term illness and a high rate of unemployment (*55*). Subjects with occupational asthma suffer increased hospitalization rates for all causes, including cardiac and respiratory disease, compared to patients without asthma but lower hospitalization rates than among patients with nonoccupational asthma at a tertiary care center (*56*). Quality-of-life questionnaires have been administered to subjects with occupational asthma and compared to

those of patients with nonoccupational asthma. Subjects with occupational asthma have statistically significant impairments in quality of life. They demonstrate increased asthma symptoms, increased limitation of activities, and increased emotional dysfunction. These clinical and functional variables may diminish with decreased severity of asthma, loss of usual job, need for job retraining, or need for early retirement (*57*).

Multiple studies have confirmed that most workers with sensitizer-induced occupational asthma do not completely recover even after cessation of exposure to the causative agent (*58,59*). Persistent nonspecific airway hyperresponsiveness is frequent and is associated with chronic airway inflammation. Risk factors for persistent asthmatic symptoms and airway hyperresponsiveness are duration of exposure, duration of symptoms before removal from exposure, and severity of asthma at time of diagnosis (*58,60*). Early removal from exposure to a sensitizer increases the likelihood of recovery, and continued exposure in sensitized workers is associated with a worsening of asthma (*61*).

With cessation of exposure, spirometry and airway responsiveness tend to improve over time. In general, spirometric measures plateau in 1 year and bronchial responsiveness plateaus in 2 years (*62*). Lemiere and colleagues (*63*) found that a majority of subjects (60%) demonstrated decreased but persistent specific airway responsiveness after removal from exposure to the offending agent. Cessation of exposure to toluene diisocyanate in sensitized workers with occupational asthma is associated with a decrease in both the number of inflammatory cells in the airway mucosa and in the amount of subepithelial fibrosis observed with serial bronchial biopsies (*64*).

Follow-up data on workers with irritant-induced asthma are sparse, but in one study a majority of pulp mill workers who developed symptoms of asthma after acute "gassing" episodes continued to have nonspecific airway hyperresponsiveness up to 2 years following their last exposures (*65*).

Impairment/Disability Assessment

Because the majority of workers with occupational asthma continue to have some degree of respiratory impairment even several years after cessation of exposure, disability (i.e., decreased ability to work in one's usual and customary job, or if severe, in any job) is a common outcome. Rates of job loss or job change are high (*66–70*). Disease severity plays a major role, but working conditions are a potent factor in determining who experiences disability and who does not (*71–73*). As a consequence of this high rate of disability, occupational asthma often has a substantial socioeconomic impact, with one study (*69*) finding that approximately 50% of affected workers suffered a reduction in income 3 years after the diagnosis was made. Physicians are often asked to assist their patients diagnosed with occupational asthma to obtain workers' compensation for any disabilities caused by the disease.

Evaluation of level of impairment due to occupational asthma should be carried out as soon as the condition has been optimally treated and stabilized. Guidelines for impairment evaluation have been developed by the American Thoracic Society and endorsed by the American Medical Association (*74,75*). These guidelines use a scoring system that involves the following categories: postbronchodilator FEV_1, reversibility of FEV_1 or degree of nonspecific airway hyperresponsiveness, and minimum asthma medication need for optimal control of the disease. Ideally, follow-up evaluation should again be carried out when there is a change in clinical status.

Prevention

Prevention must be the primary tool for decreasing the incidence of and morbidity and disability from, occupational asthma, which can become a chronic disabling disease. Prevention must involve the expertise of occupational health personnel, industrial hygienists, engineers, chemists, and allergists (*76*). It must also involve cooperation between employers, workers and their representatives, regulators, and medical personnel (*77*).

The goal of primary prevention is to prevent occupational exposure. Primary prevention methods include eliminating the sensitizing agent altogether by substitution with less hazardous substances, changing industrial processes, or reducing exposures. Secondary prevention detects asthma early so that its duration and severity can be minimized. The early detection of asthma in workers in high-risk industries such as the spray-painting industry where there is high exposure to diisocyanates is an example of secondary prevention. Tertiary prevention applies to individuals who have already been diagnosed with occupational asthma. It includes institution of appropriate health care and an effort to prevent permanent asthma by early removal of the subject from exposure (*77*). Unfortunately, although removing of workers from the vicinity of the asthma-inducing agent may lead to symptomatic improvement, it may not prevent persistent asthma.

Engineering controls may be instituted to lower the risk of exposure to irritants and sensitizers when substitutes cannot be found. Such controls include local exhaust ventilation, process enclosure, containment/isolation of hazardous exposures, and maintenance programs. Personal protective equipment such as respirators should only be considered measures of last resort. As in any industry with potential work-related hazards, proper worker education and training in work processes, safety equipment and procedures, and the use of material safety data sheets are of utmost importance.

Workplace Surveillance

Another essential component in the prevention of occupational asthma is surveillance for occupational asthma in the workplace. Surveillance programs are a type of secondary prevention in that their principal goal is the early detection of asthma. In making an earlier diagnosis, morbidity and disability can be prevented through timely intervention. Any diagnosis of occupational asthma must be considered a sentinel event; other exposed workers are at risk and need to be identified promptly (*18,40,46*).

A general approach to surveillance programs includes medical screening of co-workers as well as exposure monitoring (*40,46,77*). The former falls under the jurisdiction of a medical department, whereas the latter is performed by industrial hygiene professionals. Ideally, both the medical and industrial hygiene components should be performed in tandem. Performing surveillance in high-risk industries such as those using diisocyanates is a prime example. In medical surveillance, short symptoms questionnaires can be administered annually and should include questions about whether improvement occurs in respiratory symptoms on weekends and holidays (*40,46,77*). In addition, periodic spirometry can be performed on an annual basis and compared to baseline spirometric testing at the time of the worker's hire. Review of PEF records over several weeks can also detect workers at risk for developing occupational asthma. Industrial hygienists can perform air sampling to ensure that appropriate engineering controls are in place to protect workers. Reviewing and updating lists of agents used in a given industry should be performed on a periodic basis to identify possible asthma-inducing agents.

In Ontario, Canada, diisocyanate exposures had been the most common cause of occupational asthma in workers' compensation claims up to 1988. Subsequently initiated medical and industrial surveillance programs have resulted in earlier removal of diisocyanate-exposed workers, thus shortening the duration of their asthmatic symptoms (*78*).

Medical screening can also include skin-prick testing in high-risk industries. Skin testing is available for some HMW antigens such as flours, proteolytic enzymes, and laboratory animal proteins. Questionnaires can be administered that address allergic symptoms, skin sensitization, and respiratory symptoms.

Cross-shift spirometry can detect workers with acute work-related decrements in FEV_1 but is insensitive for detecting late responses that may occur after work hours and requires on-site medical personnel for administration of the tests. Annual methacholine challenge testing has some theoretical appeal but is impractical to apply to a large number of exposed workers.

Future Research Needs

Although much insight into the pathogenesis of sensitizer-induced asthma has been gained over the past several decades, a better understanding of the mechanism(s) underlying asthma due to exposure to LMW-sensitizing agents such as the diisocyanates is needed. Of even greater need is a data-based framework for understanding the pathogenesis of irritant-induced asthma. Development of appropriate animal models would be a major advance. Although considerable progress has been made with regard to models of HMW sensitizer-induced asthma, models of LMW sensitizer-induced asthma (*79*) and irritant-induced asthma following a single high-concentration exposure are still in a relatively early stage of development (*80*). To date, there is no model of irritant-induced asthma due to multiple lower concentration exposures.

Longitudinal studies of incident cases of asthma that are population based and allow work relatedness to be determined would provide the best approach to the question of how much asthma is due to occupational exposures. More research into potential interactions between occupational exposures and nonoccupational factors such as genetic susceptibility, smoking, and viral infections in the development of occupational asthma is also needed. Despite some important efforts with regard to HMW sensitizers (*81,82*), more exposure–response data on LMW sensitizers and irritants is critical to developing effective primary prevention programs. Development of medical surveillance protocols and interventions with documented efficacy in reducing new cases of occupational asthma in high-risk settings is a key research priority. Better data on the long-term course of irritant-induced asthma, especially the efficacy of inhaled steroids in improving outcome, would be of great value in managing patients with this condition. Finally, validation of the American Thoracic Society/American Medical Association guidelines for assessing disability due to asthma would also be an important contribution.

Summary

Occupational asthma is currently the most common form of occupational lung disease in the developed world. The prevalence of this disease is likely to remain high for many years because about 250 industrial agents are known to cause the disease and new chemicals are continuously being introduced into the workplace. Diagnosis of occupational asthma is generally established on the basis of a history that suggests a temporal association between exposure and the onset of symptoms and objective evidence that these symptoms are related to airflow limitation. Current evidence suggests that early diagnosis, elimination of exposure to the responsible agent, and early use of inhaled steroids may play important roles in preventing the long-term persistence of asthma.

Persistent occupational asthma is often associated with substantial disability and consequent impacts on income and quality of life. Prevention of new cases is the best approach to reducing the burden of asthma attributable to occupational exposures. Despite considerable advances in our understanding of occupational asthma, more research is needed on pathogenesis, risk factors, exposure–response, long-term outcome, and effective preventive strategies.

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